KRISTIN M. ABRAHAM, Ph.D., UNIV. OF MARYLAND SCHOOL OF MEDICINE $31,400

Mechanisms of *lck*-Induced Lymphoid Neoplasia

The *lck* protooncogene encodes a lymphocyte-restricted protein tyrosine kinase ($p56^{lck}$) that has been implicated in the generation of human neoplastic disease. We have produced an animal model of *lck*-induced lymphoid tumorigenesis which will permit a detailed evaluation of this process. With experiments outlined in this proposal we will define the features of this model system by analyzing biochemical changes associated with preneoplastic and tumor formation phases of disease. Using genetic strategies we will define the biochemical pathways required to maintain *lck*-associated disease, and determine what regions of $p56^{lck}$ structure contribute to its unique ability to promote lymphocyte tumor formation. By using these strategies to dissect the oncogenic function of *lck* in primary lymphocytes it will be possible to gain an understanding of the role that *src*-family protein tyrosine kinases may play in human lymphoid neoplastic disease.

ROBERT S. KRAUSS, Ph.D., MOUNT SINAI SCHOOL OF MEDICINE $31,005

Characterization and Isolation of a Secreted Factor Required for Transformation of Oncogene-Resistant Revertant Cell Lines

The transformation of a normal cell into a cancerous one involves mutations in two types of genes that play a critical role in the growth and differentiation of that cell:

1.) *proto-oncogenes*, whose functions are activated by mutation; and 2.) *tumor suppressorgenes*, whose functions are inactivated. Current evidence suggest that these genes encode components of regulatory systems that cells use to receive, transmit and respond to signals that initiate growth and/or differentiation. Although the individual functions of certain proto-oncogenes and tumor suppressor genes have been delineated, little is known about the overall control of these regulatory systems or how such controls go awry during carcinogenesis. We have isolated a panel of cell lines specifically designed to study such questions. We have started with normal rat cells and transformed them into cancerous cells by introducing into them an activated proto-oncogene (i.e., an *oncogene*). These cells have the growth properties of tumor cells. From these "transformed" cells we have further isolated rare variant cells, called *revertants*, that have regained normal growth control, despite the fact that they harbor and express an oncogene. These revertants are resistant to retransformation by a variety of different oncogenes. Several experiments suggest that these revertant cells have permanently activated a regulatory pathway that suppresses cancerous growth. We have recently found that we can specifically overcome the resistance of these revertant cells to transformation by supplying them with a small molecular weight factor secreted by normal cells. These observations suggest that this factor is required for transformation of cells by oncogenes, and that the transformation-suppressing pathway which has been activated in the revertant cells causes them to require an external supply of the factor in order to respond to oncogenes. Our goal is to purify and identify this factor, such that its role as a mediator of the effects of oncogenes can be precisely defined.